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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/574,280	03/09/2007	Jian Guan	NRNZ-01052US3	7464

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EXAMINER	
AUDET, MAURY A	

ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/574,280	GUAN ET AL.	
	Examiner	Art Unit	
	MAURY AUDET	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,14-16,21 and 25* is/are rejected.

7)☒ Claim(s) *11-13, 17-20, 22-24, and 28* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/5/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The present application is a 371 National Stage entry of PCT/US04/35165, in which this Examiner also prepared both the Search & Written Reports (Forms 210 and 237 respectively) on the identical claims 1-28 (1-24 to methods of use, 25-28 to GPE composition with at least one protease or peptidase inhibitor). The findings therein, have been carried over from the Lack of Novelty/ Inventive Step under PCT Article 33(2 or 3) and transferred nearby verbatim via the US correlational Statutory Code section 35 USC 102 or 103.

Claim Objections

Claims 11-13, 17-20, 22-24, and 28 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

> A person shall be entitled to a patent unless –

Claims 25-27 are rejected under 35 U.S.C. 102(b) as being anticipated by either Alexi (US 2002/0151522 A1) Gluckman et al. (US 2002/0027760).

Alexi teach various methods of treating neuronal cells using use of GPE and/or GPE prodrugs with i.e. pepstatin-A (see entire document, especially claims 20-21, para 0011 and 0018):

20. The method of claim 17 where the condition is a neural injury and the GPE-related compound, prodrug, or implant is first administered in the period from the time of the neural injury to 100 hours after injury, and then daily for 14 days.

Claims Text - CLTX (22):
21. The method of claim 20 where the GPE-related compound, prodrug, or implant is first administered in the period from the time of the neural injury to 8 hours after injury, and then daily for 14 days.

[0011] GPE is the tripeptide glycyl-L-prolyl-L-glutamic acid (gly-pro-glu). GPE and its dipeptide analogs GP (glycl-L-proline, gly-pro) and PE (L-prolyl-L-glutarnic acid, pro-glu) were first disclosed in EP 366638. **The suggestion has been made in EP 366638 that GPE has neuromodulatory properties. GPE has also been established as having neuroprotective properties and therefore has utility in the prevention or inhibition of neuronal and glial cell death (WO 95/17204, AU 700838). GPE has also been established as having neuromodulatory properties and therefore has utility in increasing the effective amount of choline acetyltransferase (ChAT), nitric oxide synthase (NOS), glutamic acid decarboxylase (GAD) (WO 98/14202) and tyrosine hydroxylase (WO 99/65509) in the brain.**

Detail Description Paragraph - DETX (5):
[0018] A "prodrug" of a GPE-related compound is a compound comprising the GPE-related compound and a carrier linked to the GPE-related compound by chemical bond(s) that are cleaved by biological processes within a mammal when the prodrug is administered to the mammal, such as by the action of enzyme(s) present within the mammal. Prodrugs include, for example, esters of the GPE-related compound, such as the 1-[(ethoxycarbonyl)oxy]et- hyl ester, and polypeptides that, when cleaved by a mammalian enzyme, yield the GPE-related compound. Suitable enzymes include an acid protease that generates des-(1-3) IGF-1 and GPE from IGF-1 (Yamamoto et al. (1994), Generation of des(1-3) insulin-like growth factor-I in serum by an acid protease, Endocrinology, 135(6): 2432-2439), proprotein and prohormone convertases (Seidah et al. (1999) Proprotein and prohormone convertases: a family of subtilases generating diverse bioactive polypeptides, Brain Research 848: 45-62), serum proteases, trypsin (in a calcium/magnesium-free solution), cathepsin-D, and pepstatin-A.

Gluckman et al. teach a composition of GPE and/or GPE prodrugs with i.e. pepstatin-A (see entire document, especially para 0010 and 0028):

> [0010] It is known that IGF-1 can be modified by proteolytic cleavage in nervous tissue to des 1-3N IGF-1, that is IGF-1 missing the 3 amino acids from the amino terminal of the molecule, and hence after cleavage there is also a 3 amino acid peptide gly-pro-glu which is the N terminal tripeptide. This tripeptide is also termed GPE. As des 1-3N IGF-i also binds to the IGF-1 receptor and GPE does not, GPE was thought to be of no significance to the neuronal rescue action of IGF-1. To date, there has been no enabling reference in the prior art to the manipulation of the cleaved tripeptide GPE itself to prevent or treat CNS injury or disease leading to CNS damage in vivo.
>
> [0028] A "prodrug" of a GPE-related compound is a compound comprising the GPE-related compound and a carrier linked to the GPE-related compound by chemical bond(s) that are cleaved by biological processes within a mammal when the prodrug is administered to the mammal, such as by the action of enzyme(s) present within the mammal. Prodrugs include, for example, esters of the GPE-related compound, such as the 1-[(ethoxycarbonyl)oxy]et- hyl ester, and polypeptides that, when cleaved by a mammalian enzyme, yield the GPE-related compound. Suitable enzymes include an acid protease that generates des-(1-3) IGF-1 and GPE from IGF-1 (Yamamoto et al., Endocrinology, 135(6): 2432-2439 (1994)), proprotein and prohormone convertases (Seidah et al., Brain Research, 848: 45-62 (1999)), serum proteases, trypsin (in a calcium/magnesium-free solution), cathepsin-D, and **pepstatin-A**.

Neither Alexi or Gluckman et al. does not expressly teach protecting neuronal cells "in response to a neuronal injury".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The invention is drawn to the use of the tripeptide GPE (Gly-Pro-Glu) for protecting neuronal cells from a neuronal insult and compositions comprising GPE + at least one protease or peptidase inhibitor compositions thereof.

Claims 1-10, 14-16, 21, and 25-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alexi (US 2002/0151522 A1) or Gluckman et al. (US 2002/0027760) - either alone or in view of the other.

Alexi teach various methods of treating neuronal cells using use of GPE and/or GPE prodrugs with i.e. pepstatin-A (see entire document, especially claims 20-21, para 0011 and 0018):

20. The method of claim 17 where the condition is a neural injury and the GPE-related compound, prodrug, or implant is first administered in the period from the time of the neural injury to 100 hours after injury, and then daily for 14 days.

Claims Text - CLTX (22):
21. The method of claim 20 where the GPE-related compound, prodrug, or implant is first administered in the period from the time of the neural injury

to 8 hours after injury, and then daily for 14 days.

[0011] GPE is the tripeptide glycyl-L-prolyl-L-glutamic acid (gly-pro-glu). GPE and its dipeptide analogs GP (glycl-L-proline, gly-pro) and PE (L-prolyl-L-glutarnic acid, pro-glu) were first disclosed in EP 366638. **The suggestion has been made in EP 366638 that GPE has neuromodulatory properties. GPE has also been established as having neuroprotective properties and therefore has utility in the prevention or inhibition of neuronal and glial cell death (WO 95/17204, AU 700838). GPE has also been established as having neuromodulatory properties and therefore has utility in increasing the effective amount of choline acetyltransferase (ChAT), nitric oxide synthase (NOS), glutamic acid decarboxylase (GAD) (WO 98/14202) and tyrosine hydroxylase (WO 99/65509) in the brain.**

Detail Description Paragraph - DETX (5):
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Gluckman et al. teach teach various methods of treating neuronal cells using use of GPE and/or GPE prodrugs with i.e. pepstatin-A (see entire document, especially para 0010 and 0028):

[0010] It is known that IGF-1 can be modified by proteolytic cleavage in nervous tissue to des 1-3N IGF-1, that is IGF-1 missing the 3 amino acids from the amino terminal of the molecule, and hence after cleavage there is also a 3 amino acid peptide gly-pro-glu which is the N terminal tripeptide. This tripeptide is also termed GPE. As des 1-3N IGF-i also binds to the IGF-1 receptor and GPE does not, GPE was thought to be of no significance to the neuronal rescue action of IGF-1. To date, there has been no enabling reference in the prior art to the manipulation of the cleaved tripeptide GPE itself to

prevent or treat CNS injury or disease leading to CNS damage in vivo.

[0028] A "prodrug" of a GPE-related compound is a compound comprising the GPE-related compound and a carrier linked to the GPE-related compound by chemical bond(s) that are cleaved by biological processes within a mammal when the prodrug is administered to the mammal, such as by the action of enzyme(s) present within the mammal. Prodrugs include, for example, esters of the GPE-related compound, such as the 1-[(ethoxycarbonyl)oxy]et- hyl ester, and polypeptides that, when cleaved by a mammalian enzyme, yield the GPE-related compound. Suitable enzymes include an acid protease that generates des-(1-3) IGF-1 and GPE from IGF-1 (Yamamoto et al., Endocrinology, 135(6): 2432-2439 (1994)), proprotein and prohormone convertases (Seidah et al., Brain Research, 848: 45-62 (1999)), serum proteases, trypsin (in a calcium/magnesium-free solution), cathepsin-D, and **pepstatin-A**.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use create a GPE composition with any known protease or peptidase inhibitor therein, or the use of GPE in a composition "in response to a neuronal insult" in a method of protecting/providing, to some degree, prolonged protection to neural cells in response to a neuronal some kind of insult, decreasing neural cell death or degeneration e.g. following a neuronal insult resulting from hypoxia/ischemia caused by elective surgery/stroke using the tripeptide gly-pro-glu (GPE) or GPE with at least one protease or peptidase inhibitor (i.e. peptstatin-A) in Alexi's teachings to the same (or routinely optizable forms thereof, e.g. using any known protease or peptidase inhibitor with the GPE tripeptide), in view of Gluckman et al.'s further teachings of various methods of treating neuronal cells using use of GPE and/or GPE prodrugs with i.e. pepstatin-A – the addition of the limitation of any neuronal insult is deemed anything that can lead to degeneration of the neuronal tissue, and thereby is inherently addressed by either Alexi or Gluckman et al.

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claim Rejections - 35 USC § 112 2nd

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10, 14-16, 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In e.g. claim 1, the metes and bounds of what is meant by ‘protecting neuronal cells from degenerationt' have not been sufficiently defined, leaving uncertainty as to what degree of protection and/or degeneration stoppage, the GPE composition can impute into at risk neuronal cells, to insults (?) that may cause degeneration?

In e.g. claim 1, the metes and bounds of what is meant by ‘a neuronal insult' have not been sufficiently defined, leaving uncertainty as to what insults the GPE composition can protect neuronal cell degeneration from?

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MAURY AUDET whose telephone number is (571)272-0960. The examiner can normally be reached on M-Th. 7AM-5:30PM (10 Hrs.).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MA, 3/28/09

/Maury Audet/
Examiner, Art Unit 1654